Clinical Investigation

Delta Hepatitis in Denver

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The prevalence of hepatitis D virus (HDV) infection in patients with hepatitis B virus (HBV) infection in the mid-United States is not well defined. We tested 65 patients seen between 1983 and 1986 with HBV infection in Denver for evidence of coexisting HDV infection. Five patients had anti-delta (δ) antibody. The prevalence of HDV infection was higher in patients with chronic hepatitis B (4/37) than in patients with acute hepatitis B (1/28). The prevalence of HDV infection in male homosexuals (3/32) was similar to reported figures, but the incidence of δ-infection in intravenous drug users in Denver was unusually low (1/16). In comparison to Los Angeles, New York, southern Italy, and Sweden, Denver appears to have a low incidence of HDV infection, which probably reflects its low prevalence in the drug-using population.

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Ten years ago a new hepatitis virus, the delta (δ) agent, was described.[1] The δ-agent, now known as hepatitis D virus (HDV), is a small, defective ribonucleic acid virus that depends on the hepatitis B virus (HBV) for its own replication. The broad outlines of the epidemiology of HDV infection have been drawn, but significant gaps remain. In particular, there is little information about the prevalence of HDV infection in the mid-United States. We report the incidence and epidemiologic pattern of infection with the δ-agent in Denver, Colorado.

Patients and Methods

There were two sources of patients in this study. The first was 43 patients with hepatitis B infection seen in the Hepatitis Clinic of Denver General Hospital from about November 1985 to November 1986. The second was 22 homosexual men with chronic hepatitis B infection followed by the Disease Control Service at Denver General Hospital. These patients had participated in hepatitis B prevalence and incidence studies[2] and in a hepatitis B vaccine trial.[3] Stored serum (−70°C) obtained between 1982 and 1986 was available on these patients.

Hepatitis B surface antigen (HBsAg) and immunoglobulin (Ig) M antibody to hepatitis B core antigen (anti-HBc) were measured by commercially available radioimmunoassays (Ausria II and Corab, respectively, Abbott Laboratories). IgG and IgM antibodies to the δ-agent were measured by solid-phase-capture radioimmunoassay.[4,5]

Acute hepatitis B was diagnosed on the basis of a typical clinical picture with a pronounced increase in serum aminotransferase levels and evidence of anti-HBc IgM. All but one of the 28 patients with acute hepatitis B also had HBsAg. Chronic hepatitis was diagnosed as type B on the basis of the presence of HBsAg. Acute HDV infection was diagnosed on the basis of a low titer or the absence of IgG antibody to the δ-agent and the presence of a high titer of IgM antibody to hepatitis D. Chronic HDV infection was diagnosed on the basis of a high titer of IgG antibody with a low titer of IgM antibody to the δ-agent.

Results

Of 65 patients with HBV infection, 5 had HDV superinfection (Table 1). The probable sources of hepatitis B and δ-infections were intravenous drug use (one patient), male homosexual activity (three patients), and inapparent (one patient). There were no overlapping risk factors. The intravenous drug user had acute hepatitis B and acute HDV infection. The other four patients had chronic hepatitis B and superimposed δ-infection. In two of these patients, both male homosexuals, HDV infection presented as acute hepatitis. Chronic HDV infection developed in one, resulting in chronic active hepatitis that progressed to biopsy-proved cirrhosis within two years. The other patient did not return for follow-up after his acute hepatitis subsided. The other two patients with chronic hepatitis B presented with coexisting chronic HDV infection. One was asymptomatic and had a serum aspartate aminotransferase concentration of less than twice normal. She refused liver biopsy. The second patient was mildly fatigued and had a serum aspartate aminotransferase concentration five times normal. He discontinued visits before further evaluation could be done.

Discussion

Hepatitis D virus is newly described.[1,6] It is unique in being dependent on the HBV for its own replication and survival.[6] Consequently, HDV infection only occurs in patients with coexisting HBV infection. This dual infection may take the form of acute HDV plus acute HBV infection, acute HDV infection superimposed on chronic HBV infection, or concurrent chronic HDV and chronic HBV infections. The addition of HDV infection to HBV infection increases the severity of hepatic inflammation.[6] Patients with acute δ-infection superimposed on HBV infection (either acute or chronic) frequently go on to have fulminant hepatic

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ABBREVIATIONS USED IN TEXT

anti-HBc = antibody to hepatitis B core antigen
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HDV = hepatitis D virus
Ig = immunoglobulin

failure.[4,6,7] Patients with chronic HBV and δ-agent infections usually have chronic active hepatitis progressing to cirrhosis.[6-9]

A general outline of the worldwide epidemiology of HDV infection has taken shape in the decade since the first description of the δ-antigen and antibody system (Table 2). HDV infection complicates hepatitis B virus infection with a relatively high frequency in Italy and Scandinavia. A high incidence of HDV infection has been described among Indians in Venezuela and natives of Northwest Kenya. Infection with the δ-agent is relatively infrequent throughout Asia and in Australia.

In the United States, surveillance of patients with hepatitis B infection for HDV superinfection has mainly been done in large urban centers on the East and West coasts (Table 2). These areas, in particular California and New York, have had relatively high incidences of HDV infection. In surveys of HBsAg-positive blood donors throughout the United States, δ-antibodies were found in 4% of subjects.[10] The highest frequency (12%) was in San Jose, California, and the lowest in the south-central states (1%). These figures probably somewhat underestimate the frequency of δ-infection in this country. HDV infection usually produces severe hepatocellular injury, and acceptable volunteer blood donors have no history of liver disease. The present report, however, documents only a slightly higher incidence of HDV infection

TABLE 1.—*Prevalence of Hepatitis D Virus Infection in Denver, 1982-1986*

Patient Source	*Hepatitis Clinic*		*Disease Control Service*
Period of surveillance	1985-1986		1982-1986
Type of infection	Acute	Chronic	Chronic
Source of infection*			
Male homosexual	0/4	1/6	2/22
Intravenous drug use	1/12	0/4	0
No obvious source	0/10	1/4	0
Miscellaneous†	0/2	0/1	0
Totals	1/28	2/15	2/22

*The numbers indicate persons with the δ-agent/patients with hepatitis B.
†Transfusion (1) and birth in an endemic area (Vietnam, 1).

TABLE 2.—*Epidemiology of δ-Infection*

Location	*Source*	*Period of Surveillance*	*Acute HBV Infection**	*Chronic HBV Infection**
Italy	Rizzetto et al, 1979[9]	NS	...	48/227
	Raimondo et al, 1982[11]	1979-1981	63/98†	41/63†
	Smedile et al, 1983[12]	1978-1981	99/687	238/1,314
	Arico et al, 1985[13]	1981-1984	...	112/2,487‡
	Maggiore et al, 1985[14]	1974-1982	...	13/102§
France	Rizzetto et al, 1980[15]	NS	...	1/92
Germany	Rizzetto et al, 1980[15]	NS	...	3/153
Poland	Rizzetto et al, 1980[15]	NS	...	1/50
Switzerland	Raimondo et al, 1982[11]	1974-1981	6/17†	5/16†
Greece	Tassopoulos et al, 1986[16]	NS	...	4/167
Scandinavia	Rizzetto et al, 1980[15]	NS	...	9/19
	Hansson et al, 1982[17]	1970-1981	...	41/57
	Raimondo et al, 1982[11]	1974-1981	3/7†	5/11‡
	Lindh et al, 1986[18]	NS	...	15/60
	Hess et al, 1986[19]	NS	...	2/44‖
Ireland	Raimondo et al, 1982[11]	1974-1981	15/49†	...
Great Britain	Weller et al, 1983[20]	NS	...	9/71
Taiwan	Rizzetto et al, 1980[15]	NS	...	4/53
Japan	Rizzetto et al, 1979[10]	NS	...	2/86
	Rizzetto et al, 1980[15]	NS	...	2/152
Australia	Rizzetto et al, 1980[15]	NS	...	1/21
Kenya	Thomas, 1985[21]	NS	...	NS (65%)
Venezuela	Hadler et al, 1984[22]	1981-1982	...	47/83
USA, NJ	Rizzetto et al, 1979[10]	NS	...	8/25
NJ	Rizzetto et al, 1980[15]	NS	...	8/35
NY	Rizzetto et al, 1979[10]	NS	...	5/24
Mass	Jacobsen et al, 1985[23]	1976-1984	6/114	15/110
Md	Rizzetto et al, 1980[15]	NS	...	0/81
Calif	Rizzetto et al, 1980[15]	NS	...	13/40
Calif	De Cock et al, 1986[24,25]	1967-1985	17/358	45/200
Minn	Shiels et al, 1985[26]	1969-1983	1/68	28/464
Colo	Present report	1983-1986	1/28	4/37

HBV=hepatitis B virus, NS=not stated

*The number with infection with the δ-agent versus the number with HBV infection.
†Intravenous drug users.
‡Asymptomatic carriers.
§Children.
‖Male homosexuals.

in patients with clinically evident hepatitis B in Denver (5/65, 8%).

Antibodies to HDV frequently rise late in the course of acute HDV infection.[6] Arguably, our estimate of the frequency of HDV coinfection in patients with acute hepatitis B could be falsely low. Such patients were typically seen first in primary care facilities, however, and had reached the peak of their illness or were in the convalescent phase when a serum specimen was drawn in the Hepatitis Clinic for HDV antibodies. Consequently, the number of false-negative diagnoses was probably minimal.

HDV infection appears to be transmitted most efficiently by the parenteral route.[6] Most centers have reported the highest incidences in persons with hemophilia and in intravenous drug users.[9,11,12,15,17,20] The HDV is infrequently transmitted by male homosexual activity. We found a 10% incidence of HDV infection in homosexual men with HBV infection. This is comparable to other reported figures.[19,24] In contrast, the incidence of HDV infection in intravenous drug users in Denver (1/16) is considerably lower than that cited in most other reports.[9,11,12,15,17,20] HDV coinfection rates in this group have been rising steadily in Sweden.[17] The relative infrequency of HDV infection in Denver at present may indicate only that we are in the early stages of a developing epidemic. Continued surveillance will be necessary to define secular trends.

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